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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,356	01/26/2005	Christopher Bruce Alexander Whitelaw	102286.155US1	1380

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WILMERHALE/BOSTON
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/21/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/522,356	WHITELAW ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,23,25-28,30,31,33 and 36-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,23,25-28,30,31,33 and 36-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-11-08 has been entered.

Applicants' amendment filed 11-11-08 has been entered. Claims 22 and 33 have been amended. Claims 24, 32, 34 and 35 have been canceled. Claims 36-44 have been added. Claims 22, 23, 25-28, 30, 31, 33 and 36-44 are pending and under consideration.

It is noted that SEQ ID No. 1 which is EQKLISEEDL from c-myc and promoter element Cypla1 are considered in view of the election filed 5-29-07.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 26, 27, 40 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "the method of claim 24" in claim 26 is vague and renders the claim indefinite. Claim 24 has been canceled. Claim 26 depends from a canceled claim. It is unclear what is intended in the claim. Claim 27 depends from claim 26.

The phrase "the method of claim 40" in claim 40 is vague and renders the claim indefinite. Claim 40 depends from itself. It is unclear what is intended for the phrase "the method of claim 40".

The phrase "the method of claim 43" in claim 43 is vague and renders the claim indefinite. Claim 43 depends from itself. It is unclear what is intended for the phrase "the method of claim 43".

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22, 23, 25-28, 30, 31, 33 and 36-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on transgenic mouse or rat and its use for detecting and screening a gene activation event of toxicologically induced stress. The claims encompass the use of transgenic mice or rats comprising a construct comprising a nucleic acid sequence encoding a beta-lactoglobulin (BLG) under the control of Cyp1a1 promoter and a nucleic acid sequence encoding a peptide sequence having the sequence of SEQ ID No. 1, and having various unknown and unidentified phenotypes. The specification fails to disclose any transgenic mouse or rat having

any particular phenotype and said transgenic mouse or rat can be used for detecting and screening the claimed gene activation event. The specification fails to disclose the structural feature or phenotype of the claimed various transgenic mice and rats. The structural features and phenotypes of the transgenic mice and rats that can distinguish said transgenic mice or rats from wild-type animals have not been disclosed. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify the claimed transgenic mice or rats, and because the claimed transgenic mice or rats are highly variant, the information as disclosed in the present application is insufficient to describe the claimed transgenic mice and rats and their uses.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed transgenic mice and rats. Thus, it is concluded that the written description requirement is not satisfied for the transgenic mice and rats and their uses as claimed.

Applicants argue that the claims have been amended to read on transgenic mouse and rat and detecting the gene activation event of a peptide tagged beta-lactoglobulin reporter gene (amendment, p. 9-10). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph written description rejection.

6. Claims 22, 23, 25-28, 30, 31, 33 and 36-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considered whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirement, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d at 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention with function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raises and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims are drawn to a method of detecting a gene activation event in vivo by assaying a transgenic mice or rats whose cells express a construct comprising a nucleic acid sequence encoding a beta-lactoglobulin (BLG) under the control of Cyp1a1 promoter and a nucleic acid sequence encoding a peptide sequence having the sequence of SEQ ID No. 1, wherein the animal is subjected to a gene activation event of toxicologically induced stress, and a

method of screening for, or monitoring of toxicologically induced stress by using said transgenic mice or rats.

The claims read on transgenic mice or rats and its use for detecting and screening a gene activation event of toxicologically induced stress. The claims encompass the use of transgenic mice or rats comprising a construct comprising a nucleic acid sequence encoding a beta-lactoglobulin (BLG) under the control of Cyp1a1 promoter and a nucleic acid sequence encoding a peptide sequence having the sequence of SEQ ID No. 1, and having various unknown and unidentified phenotypes.

The specification only discuss using one of several standard methods including pronuclear injection, blastocyst injection of transfected cells or using viral vector to generate transgenic animals. Preparation of vector pXC3'mycBLG and the use of said vector to produce transgenic animals (Example 11, p. 48-49). The specification fails to generate any transgenic animals, such as mice or rats. The specification fails to provide adequate guidance and evidence for what would be the phenotype of the transgenic mice or rats and whether said transgenic mice or rats can be used for detecting and screening gene activation event of toxicologically induced stress as claimed.

The claims encompass using numerous different transgenic mice or rats to detect and screen toxicologically induced stress in vivo. Applicants do NOT have possession of any transgenic mice or rats, therefore, one skilled in the art at the time of the invention would not know how to use various transgenic mice or rats for the claimed method. It is noted that claims 30 and 42 specify "a stress inducible promoter which is operably isolated from a nucleic acid sequence encoding beta-lactoglobulin" and the phrase "operably isolated" means the opposite of

"operably linked", therefore, the promoter does not control the expression of the gene (see page 11, 1st full paragraph of the amendment filed 5-14-08). Since the stress inducible promoter is **operably isolated** from a nucleic acid sequence encoding beta-lactoglobulin, it is conceivable that the stress inducible promoter will NOT control the expression of beta-lactoglobulin. Thus, the expression of beta-lactoglobulin would NOT be induced by the stress inducible promoter which in turn can be induced by toxicological stress. The specification fails to provide adequate guidance and evidence for how to detect a gene activation event in a transgenic mouse or rat when a toxicological stress induces a stress inducible promoter but said stress inducible promoter can NOT induce expression of the reporter gene beta-lactoglobulin.

Further, the state of the art of transgenics at the time of the invention held that the resulting phenotype of transgenic animals was unpredictable. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Wall, R. J., 1996 (Theriogenology, Vol. 45, p. 45-68) states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (e.g. p. 61, last paragraph), and "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies" (e.g. p. 62, first paragraph). In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) points out that reintegration of an isolated gene into the genome of an animal by gene microinjection may generate complex and

unpredictable biological situations (e.g. p. 146, first paragraph). Houdebine states that "animal transgenics is still suffering from technical limitations" (e.g. abstract).

In addition, the genetic background of the transgenic animal has a large impact on the resulting phenotype of the transgenic animal. Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction).

The claims encompass using different beta-lactoglobulin derived from various organisms. Different beta-lactoglobulin proteins have different amino acid sequences. The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution

results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, the biological function of protein was unpredictable at the time of the invention and different beta-lactoglobulin could have different biological functions, which adds to the unpredictable resulting phenotype of the transgenic mice or rats expressing various beta-lactoglobulin proteins.

Since resulting phenotype of the transgenic mice or rats expressing the claimed construct was unpredictable at the time of the invention, one skilled in the art at the time of the invention would not know whether the claimed transgenic mice or rats would have any phenotype and whether the phenotype, if any, would be distinguishable from the wild type animals, and whether said transgenic mice or rats could be used for detecting and screening the gene activation event of toxicologically induced stress. The specification fails to provide guidance and evidence for what cells, tissues or sample from the transgenic mice or rats would be able to express the beta-lactoglobulin under toxicological stress and can be used to detect the claimed gene activation event. In addition, the claims fail to recite how to induce stress, what agent or method is used to induce stress, what is screened, and how to determine the toxicologically induced stress occurs.

Absent specific guidance and evidence, one skilled in the art at the time of the invention would not know how to use the claimed transgenic mice or rats for detecting and screening the gene activation event of toxicologically induced stress as claimed.

The specification contemplates using blastocyst injection of transfected cells to generate transgenic rats. Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). Gene replacement by homologous recombination in somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells" (e.g. p. 148, right column). However, gene transfer or inactivation using embryonic cells has failed in species other than mouse, and "the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line...The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines to consider that the so-called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course" (e.g. p. 149, left column). It appears only two mouse ES cell lines can be used to generate transgenic mice and no other known ES cell lines have been established to generate any other transgenic animals, such as rats.

In view of the lack of ES cells other than the mouse ES cells for making transgenic animals, the inherent unpredictability of the resulting phenotypes of various transgenic mice or rats comprising the claimed construct and the influence of the genetic backgrounds of different animals on the resulting phenotype, one skilled in the art at the time of the invention would not

know how to make and/or use the transgenic mice or rats having the claimed construct and exhibiting various unknown and unidentified phenotypes, and how to use said transgenic mice or rats for detecting and screening gene activation event of toxicologically induced stress.

The breadth of claims also encompasses chimeric mice or rats containing cells comprising the claimed construct. The specification fails to enable making chimeric mice or rats such that they exhibit expression of the claimed construct. The specification does not correlate chimeric mice or rats, comprising cells with the claimed construct to any phenotype. The method of making genetic mosaic animal is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes. This ratio cannot be predetermined. Furthermore, the spatial distribution of cells of each genotype cannot be predetermined. Therefore, the phenotype of chimeric animals is not only dependent upon the genotype of the cells (which is unpredictable as set forth by the state of the art outlined above, for example see Kappel; Sigmund) but is also dependent upon the spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric mice and rats encompassed by the claims is highly unpredictable. The specification fails to provide the guidance necessary to overcome this high level of unpredictability to generate a chimeric mouse or rat exhibiting any specific phenotype or any phenotype other than wild type. As set forth above, without a predictable phenotype, it would require additional and undue experimentation for one of skill in the art at the time of the invention to determine the use of a chimeric mouse and rat comprising the claimed construct.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the

level of one of ordinary skill which is high, the amount of the experimentation required and the breadth of the claims that it would require undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed.

Applicants argue that the claims have been amended to read on transgenic mouse and rat and the specification teaches the method of monitoring toxicologically induced stress in a transgenic mouse or rat (amendment, p. 9-10). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph enablement rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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